THE EFFECTS OF TIME-VARYING BLOOD FLOW ON DIFFUSIONAL RESISTANCE TO OXYGEN TRANSFER IN THE PULMONARY CAPILLARIES

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ABSTRACT The effects of the persistence of pulsatile blood flow in the pulmonary capillaries on the over-all diffusing capacity and alveolar-arterial oxygen tension gradient were studied. A mathematical analysis was made of the oxygen transfer process using an undamped cardiac flow pulse in the capillaries and taking into account the finite rate of reaction of oxygen with hemoglobin.

In five cases of both normal and low oxygen atmospheres, combined with varying degree of exercise, it was found that the alveolar-arterial oxygen tension gradients were not affected by the time-varying blood flow, while in cases of breathing air the over-all diffusing capacity of the lung increased 10–15% over the diffusing capacity obtained with constant blood flow rate in the pulmonary capillaries.

INTRODUCTION

The transport of oxygen from the alveolus to pulmonary capillary blood brings about a change in the oxygen concentration of each volume of blood as it flows down the pulmonary capillary. The ease or difficulty of this diffusional transport of oxygen to the red blood cells, and the reaction of oxygen with hemoglobin determines the shape of the plot of oxygen tension in the red cells vs. distance down the capillary, as well as the point in the capillary at which the blood oxygen tension reaches that of alveolar air. Resistance to diffusion of oxygen is met at the alveolo-capillary membrane, in the blood plasma, at the wall of the erythrocyte, and in the finite rate of reaction of oxygen with hemoglobin. The resistances to diffusion, coupled with the flow rate of blood in the pulmonary capillaries, determine the final oxygen saturation of blood as it leaves the capillaries.

The first mathematical treatment of the time course of blood oxygenation in the pulmonary capillaries was given by Bohr (2). In the Bohr model, the capillary was

viewed as a rigid tube with blood flowing through at a constant rate. Oxygen was assumed to encounter diffusional resistance at the capillary wall, but then to react instantaneously with the hemoglobin in the erythrocytes. Using the oxy-hemoglobin dissociation curve and knowing the end-capillary oxygen saturation, the relation of oxygen tension in the blood to the time of exposure to alveolar gas was determined by a straightforward mathematical procedure which is now called the "Bohr integration" (7). A recent use of this basic calculation is given by Milhorn and Pulley (12) in a study of pulmonary gas exchange and the effects of venous admixture on the respiratory process.

A modification of the "Bohr integration" was made by Staub, Bishop, and Forster (17), who took into account the fact that the rate of reaction of oxygen with hemoglobin is not instantaneous, but is one of the limiting factors in the oxygenation process. Using oxygen-hemoglobin reaction rate data (20) and end-capillary alveolar-arterial oxygen tension gradient data (14), the oxygen tension of the blood was found as a function of the time of exposure to alveolar gas.

Later, Crandall and Flumerfelt (5) investigated the effect of time-varying blood flow on the oxygenation process, using oxygen-hemoglobin reaction rate data and end-capillary data identical to Staub, Bishop, and Forster (19), while further assuming a form for the blood pulse in the pulmonary capillaries.

Staub (16) took a different approach to the analysis of oxygen uptake in the capillaries, using data compiled from various workers (1, 9) for the membrane diffusing capacity of oxygen ($D_{M_{O_2}}$) and the volume of blood in the capillaries (V_c), instead of end-capillary gradient data. The results of calculations were then the total diffusing capacity of the lung ($D_{L_{O_2}}$) and the end-capillary alveolar-arterial oxygen tension gradient (a-AD). These calculations were made using a constant blood velocity.

The purpose of this paper is to compare the results obtained from the time-varying blood flow model with those obtained from the constant velocity model when $D_{M_{O_2}}$ and V_c (instead of end capillary) data are used in both models.

PRESENTATION OF TIME VARYING MODEL

The details of the derivation of the equations governing oxygen transport into capillary blood under varying flow rate conditions have been given previously (5). For the sake of continuity and comparison the final equations obtained by Crandall and Flumerfelt will be summarized here.

The partial differential equation relating oxygen tension in the red blood cell, P_{RBC}, to distance down the capillary, x, and time since the beginning of the heartbeat, t, is

$$\frac{\partial P_{RBC}}{\partial t} + u(t)\frac{\partial P_{RBC}}{\partial x} = f(P_{RBC})\frac{(P_A - P_{RBC})\,D_{L_{O_2}}}{V_c - \alpha_e} \qquad (1)$$

where $u(t)$ is a specified blood velocity function. It should be pointed out that both $D_{L_{O_2}}$ and α_s are functions of P_{RBC}.

The solution to equation 1 is given as (5)

$$\int_0^{t-\int_{P_v}^{P_{RBC}} \frac{dP}{f(P)}} u(t)\,dt = \int_0^t u(t)\,dt - x. \qquad (2)$$

The assumptions inherent in the time varying model are presented and discussed by Crandall and Flumerfelt (5). Identical assumptions are used in our work. It is to be noted, however, that the one dimensional model of the pulmonary gas exchanging apparatus represented by equation 1 is not a model in the physical sense. Equation 1 models a *functional* aspect of the pulmonary microcirculation; that is, there is an average value of the path length that blood travels while exposed to alveolar air. This average path length is called "the length of a pulmonary capillary" where a pulmonary capillary is visualized as a rigid tube with a given fixed volume. This visualization need have no physical relationship to actual structure. If the model is to *function* as the actual pulmonary gas exchanging apparatus, the actual variation in path lengths around the mean path length must be small.

The model was applied to a lung functioning under five different combinations

TABLE I

SUMMARY OF DATA USED*

	Case (1)	Case (2)	Case (3)	Case (4)	Case (5)
Alveolar oxygen tension, *mm Hg*	100	47	55	120	59
Venous oxygen tension, *mm Hg*	41.5	33.9	19.4	13.5	15.5
Membrane diffusing capacity	112	112	120	144	144
Period of heartbeat, *sec*	0.682	0.566	0.444	0.324	0.324
Volume of capillaries, *ml*	86	86	119	152	152
Capillary transit time, *sec*	0.760	0.636	0.476	0.496	0.304
Constant velocity of the red blood cells, *cm/sec*	0.0656	0.0785	0.1050	0.1005	0.1643
Cross sectional area for flow, cm^2	1720	1720	2380	3040	3040
Total blood flowrate, *liter/min*	6.8	8.1	15.0	18.4	30.0
Stroke volume, *ml*	77	76	111	100	162

* Case (1)-rest, air; case (2)-rest, low oxygen; case (3)-moderate exercise, low oxygen; case (4)-heavy exercise, air; and case (5)-heavy exercise, low oxygen.

of atmospheric oxygen content and exercise levels, as outlined by Staub (16), and given by the column headings of Table I.

DATA

Instantaneous oxygen tension profiles in the pulmonary capillary were generated on a computer by use of equation 2 and input data describing each of the five cases, employing as a numerical scheme a modified Newton-Raphson technique (10). α_e as a function of P_{RBC} was obtained by using the method given by Crandall and Flumerfelt (5). Although the equation of Roughton and Forster (15) was used,

$$\frac{1}{D_{L_{O_2}}} = \frac{1}{D_{M_{O_2}}} + \frac{1}{V_c \cdot \theta_{O_2}} \tag{3}$$

there are two distinct choices as to the basic data to be used. In one, the measurements of the end-capillary alveolar-arterial oxygen tension gradient are assumed to be correct, and $D_{M_{O_2}}$ and V_c are calculated. This is the approach taken by Crandall

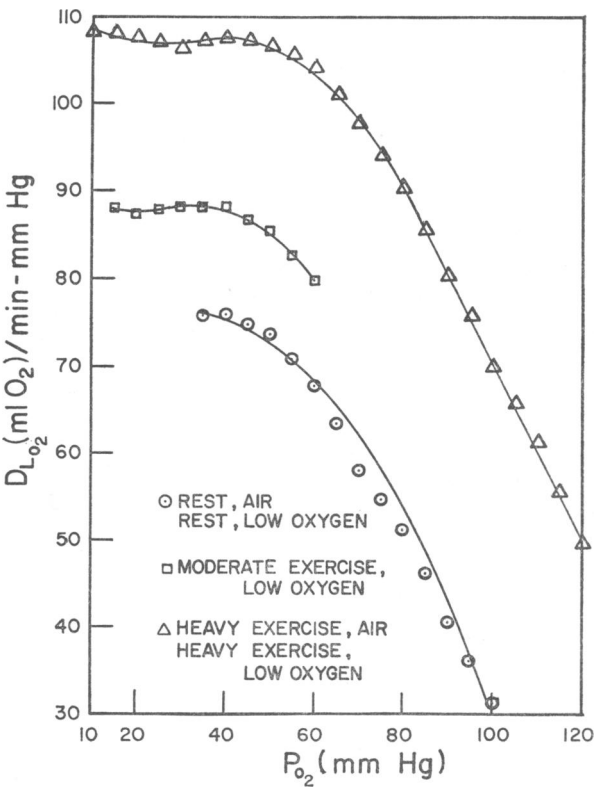

FIGURE 1 Over-all diffusing capacity of the lung ($D_{L_{O_2}}$) for cases (1)–(5). Calculated from $1/D_{L_{O_2}} = 1/D_{M_{O_2}} + 1/\theta_{O_2}V_c$.

and Flumerfelt (5). In the other, the measurements of $D_{M_{O_2}}$ and V_c are assumed to be correct, and the oxygen tension profile and the end-capillary alveolar-arterial gradient are calculated. This is the approach taken in the present work.

Although none of the data are known well enough and there is considerable scatter in reported values, the data for $D_{M_{O_2}}$ and V_c compiled by Staub (16) were taken. The use of $D_{M_{O_2}}$ and V_c data as basic seems to be a more logical approach to calculation of capillary oxygen tension profiles because (*a*) there is considerable difficulty in measuring the end-capillary oxygen tension gradient experimentally (8, 16), whereas single breath carbon monoxide measurements are straight forward and based on reasonable assumptions of the similarity of the diffusion of carbon monoxide and oxygen through the tissue (7), and (*b*) it is known (9, 16) that the experimental measurement of $D_{M_{O_2}}$ and V_c are less influenced by a nonideal ventilation-perfusion ratio than the measurement of the end-capillary gradient. Therefore, the use of $D_{M_{O_2}}$ and V_c seems more appropriate for a study of diffusion and reaction in the oxygenation process. The plot of $D_{L_{O_2}}$ as a function of oxygen tension is given in Fig. 1 for each of the five cases examined in this study.

To complete the specification of $f(P_{RBC})$ the data for $\theta_{O_2}(P)$ and P_A as given by Staub (16) were used. The use of a constant value of alveolar oxygen tension seems to be a good assumption for all cases of this study. For a normal oxygen atmosphere, the variation in alveolar oxygen tension is slight compared with the average alveolar-blood oxygen tension gradient along the capillary. In a study of a coupled model

TABLE II

COMPARISON OF RESULTS FOR CONSTANT VELOCITY AND VARYING VELOCITY

Cases	Average total diffusing capacity for the lung ($D_{L_{O_2}}$)		Alveolar-arterial end capillary oxygen tension gradient (*a-AD*)	
	Constant velocity	Varying velocity	Constant velocity	Varying velocity
	ml O_2/min — mm Hg		*mm Hg*	*mm Hg*
(1) Rest, air	33.1	38.8	<0.1	<0.1
(2) Rest, low oxygen	74.5	75.6	0.2	0.2
(3) Moderate exercise, low oxygen	87	86.9	4.0	4.0
(4) Heavy exercise, air	62.8	70.4	<0.1	<0.1
(5) Heavy exercise, low oxygen	108	108	16.0	18.0

of the human respiratory system, Crandall and Flumerfelt (4) concluded that even in low oxygen cases the variation in alveolar oxygen tension has only negligible effects on alveolar-arterial gradients. Thus, $f(P_{RBC})$ is known as a function of P_{RBC} in the range P_v to P_A in each of the five cases of Table II.

To facilitate computer calculations, the ratio $D_{L_{O_2}}/\alpha_e$ was represented as a second order polynomial (5)

$$\frac{D_{L_{O_2}}(P_{RBC})}{\alpha_e(P_{RBC})} = C_1 + C_2 P_{RBC} + C_3 P_{RBC}^2, \qquad (4)$$

The constants C_1, C_2, and C_3 were determined by a least squares fit using data points generated at oxygen tensions at which data for $\theta_{O_2}(P)$ were given by Staub (16). The choice of the basic data discussed earlier shows up a fundamental difference in the D_L/α_e between the earlier work (5) and the present one. Comparison of the Fig. 1 from Crandall and Flumerfelt (5) with the Fig. 2 of the present work shows that the former gives two separate curves for D_L/α_e, one for a subject resting and breathing a normal oxygen atmosphere and another for a subject resting and breathing a low oxygen atmosphere, (these cases correspond to cases (1) and (2) of this study), whereas, the latter shows that cases (1) and (2) share the same curve for D_L/α_e, but operate on different pressure ranges of that curve. This is due to the invariance of both $D_{M_{O_2}}$ and V_c with inspired oxygen content, as found by single breath carbon monoxide measurements. Table II shows that $D_{M_{O_2}}$ and V_c vary with exercise level rather than inspired oxygen content. For cases (3), (4), and (5) the plots of D_L/α_e are given in Figs. 3 and 4.

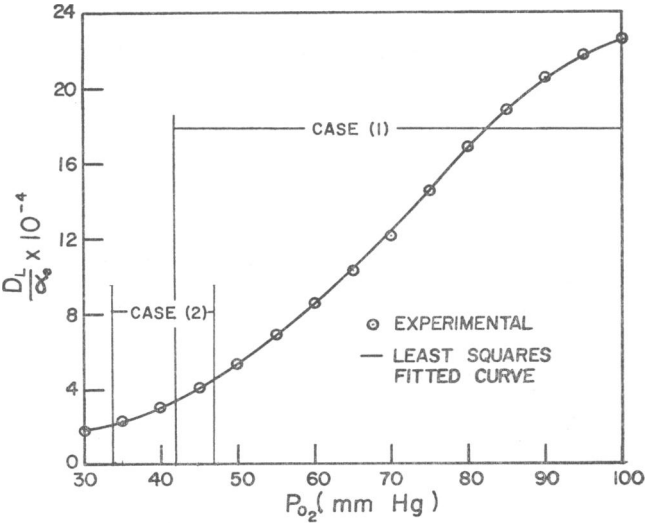

FIGURE 2 D_L/α_e for rest (cases (1) and (2)).

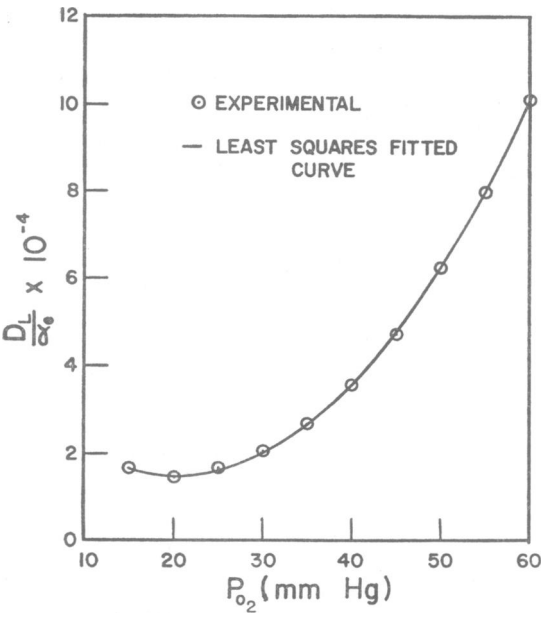

FIGURE 3 D_L/α_e for moderate exercise (case (3)).

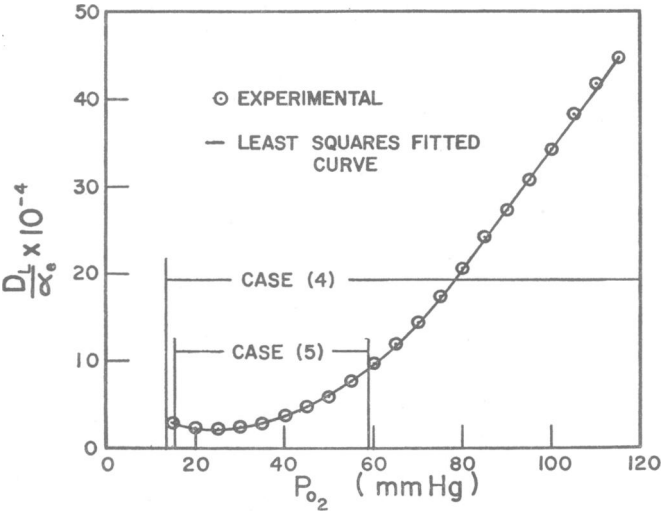

FIGURE 4 D_L/α_e for heavy exercise (case [4] and case [5]).

The form of the blood velocity (and hence flow rate) in the pulmonary capillaries was specified as (5, 13)

$$u(t) = \frac{Ka}{A}\frac{t}{t_c}e^{-a\frac{t}{t_c}}. \tag{5}$$

Although little quantitative information is available on the shape of the blood flow pulse in the microcirculation, there is good evidence (3, 11, 21) that flow is pulsatile. Wiener, et al. (21) have done a mathematical analysis of wave propagation in the pulmonary circulation, concluding that the period of the flow pulse in the capillaries is approximately that of the heartbeat.

By adjusting the parameters K and a in equation 5 a waveform characteristic of the undamped output pulse of the right ventricle may be obtained. The findings of Wiener, et al. (21) indicate that the flow pulse is attenuated slightly and that the flow lasts over a longer portion of the heartbeat in the capillaries than in the pulmonary arteries. Considering the openness of the question of the existence of pulsatile flow in the pulmonary capillaries, this difference was neglected. At any rate an undamped flow pulse represents the extreme case, and the results of calculations using an undamped waveform will give the greatest possible effect of pulsatile flow. As noted previously (5) the actual case is probably somewhere between undamped flow and constant flow. A plot of equation 5 is given in Fig. 5.

The value for the average length of path of the blood in the pulmonary capillaries was taken from the extensive morphological studies of Weibel (19). In this study, as in the previous study with the time-varying flow rate model (5) a path length of 500 μ was assumed. Data used in this work is summarized in Table I.

As a basis of comparison with constant velocity model, the oxygen tension was

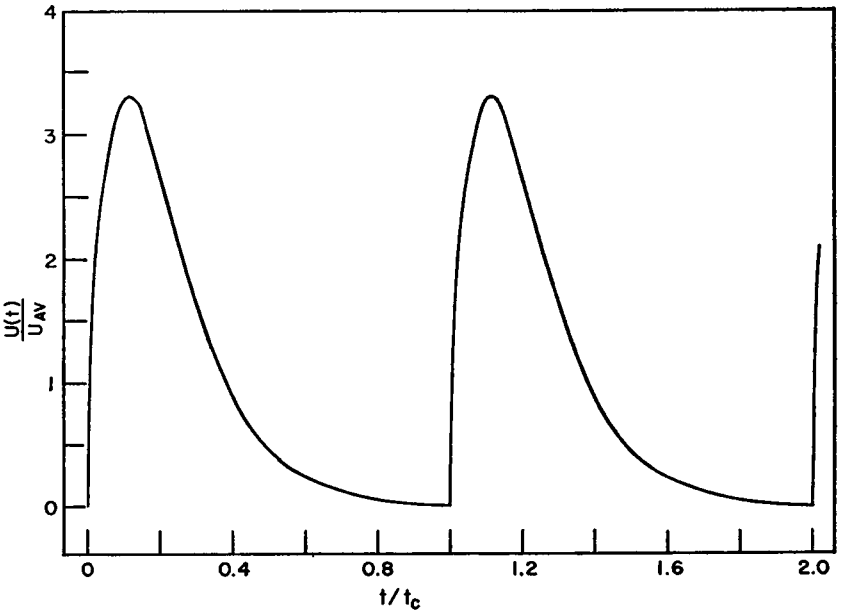

FIGURE 5 Dimensionless linear blood velocity in pulmonary capillaries (equation 5) vs. dimensionless time (fraction of the period of the hearbeat).

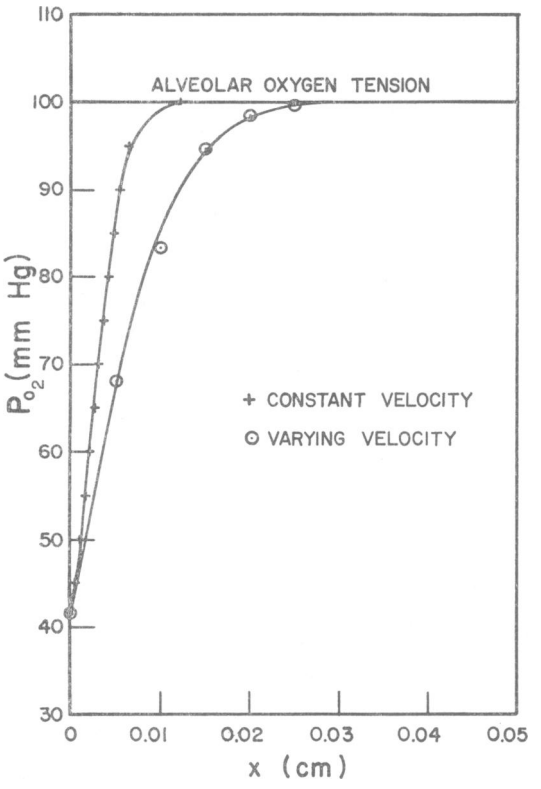

FIGURE 6 Average oxygen tension profiles for constant and time-varying flow rates, case (1)—at rest, normal oxygen atmosphere.

"bulk" averaged according to the formula

$$P_{RBC}(x) = \frac{\int_0^{t_c} u(t)P(x,t)\,dt}{\int_0^{t_c} u(t)\,dt}. \tag{6}$$

The plots of the average P_{RBC} of equation 6 vs. x are given in Figs. 6–10 for each of the cases (1)–(5) in Table I. Also plotted are the results for constant velocity blood flow for each case. The over-all diffusing capacity for the lung ($D_{L_{O_2}}$) was calculated using the formula

$$\bar{D}_{L_{O_2}} = \frac{\int_0^{0.05} D_{L_{O_2}}[P(x)]\,dx}{\int_0^{0.05} dx}. \tag{7}$$

The results for constant velocity cases are compared with the results for varying velocity cases in Table II.

DISCUSSION OF RESULTS

Table II shows that in all of the cases examined in this study, the pulsatile nature of capillary flow does not significantly alter the alveolar-arterial oxygen tension gradient from that found for the constant velocity model. However, the results for the average diffusing capacity of the lung are affected by a time-varying velocity in certain cases. In the low oxygen atmosphere, at rest, with moderate exercise, or with heavy exercise, diffusing capacities are very nearly equal for constant and pulsatile flow. In air at rest or with heavy exercise, the varying velocity model yields diffusing capacities 10–15% higher than those with the constant flow model. The reason for this behavior may be understood in terms of Figs. 6–10 and Fig. 1, which is the plot of D_{LO_2} vs. P_{O_2} for each of the cases (1)–(5). For low oxygen cases the D_{LO_2} values obtained from the two models compare well because the constant velocity and varying velocity curves in Figs. 7, 8, and 10 match so closely. In air the concentration profiles differ significantly (Figs. 6 and 9). In each of these cases the effect of the time varying blood flow is to make the rise in oxygen tension more gradual over the tube length; that is, making the average tension in the capillary

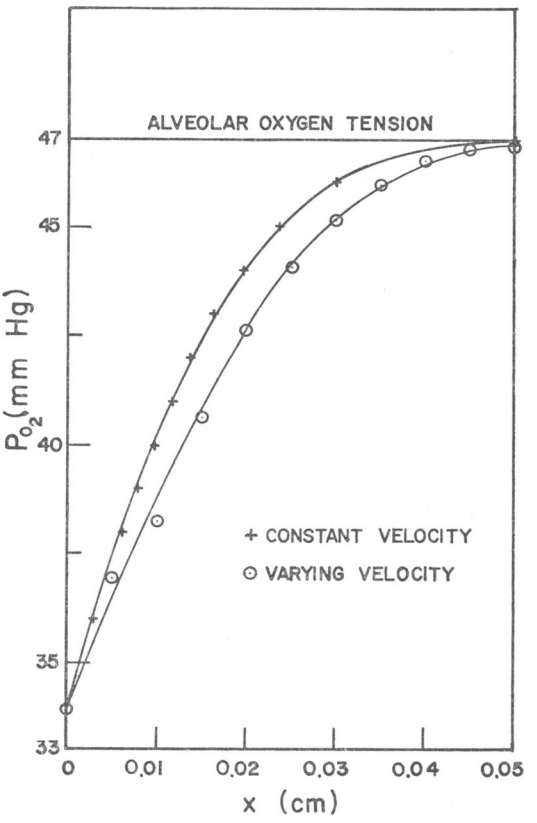

FIGURE 7 Average oxygen tension profiles for constant and time-varying flow rates, case (2) —at rest, low oxygen atmosphere.

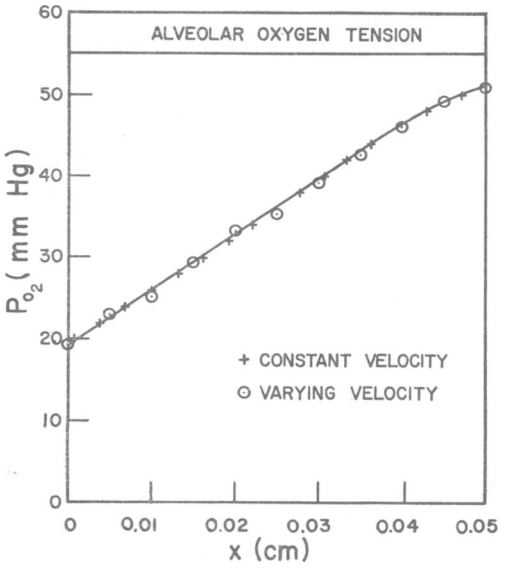

FIGURE 8 Average oxygen tension profiles for constant and time-varying flow rates, case (3)—moderate exercise, low oxygen atmosphere.

lower. In Fig. 1 it can be seen that the lower the oxygen tension, the greater the diffusing capacity, which explains the rise in $D_{L_{O_2}}$ for the varying flow rate case.

The very close agreement between the constant and varying velocity curves in cases (2), (3), and (5) is a result of the large value of $D_{L_{O_2}}$ and oxygen tension gradient for low oxygen respiration. The diffusing capacities of cases (2) and (5) in low oxygen are almost twice those for the same amount of exercise in air (cases (1) and (4)), and this increase hides the effect of varying velocity which can be seen in cases (1) and (4).

Also included in Fig. 11 are the instantaneous oxygen tension profiles for case (3) which are representative of all other cases. The profiles clearly show the advance of the front of a slug of venous blood in the capillary by the abrupt jumps in oxygen tension for the profiles at $t = 0.2t_c$ and $t = 0.4t_c$. Once this slug has reached the end of the capillary, blood flow is slower and the tension rises more uniformly over the whole capillary length, returning to the original curve for $t = 0$ when the period of the heartbeat has passed. Because of this kind of transient behavior it may be deduced that on the average, pulsatile capillary flow will produce a lower oxygen tension throughout the capillary (or a larger gradient) than will constant velocity. In breathing air, as has been previously stated, this effect may be seen in the resultant "bulk average" curves derived from the instantaneous concentration profiles, while in low oxygen the larger diffusing capacity of the red blood cells renders this effect insignificant.

Final conclusions as to the effect of pulsatile flow in the capillaries on gas exchange must wait until the unevenness of ventilation and perfusion in the lung is

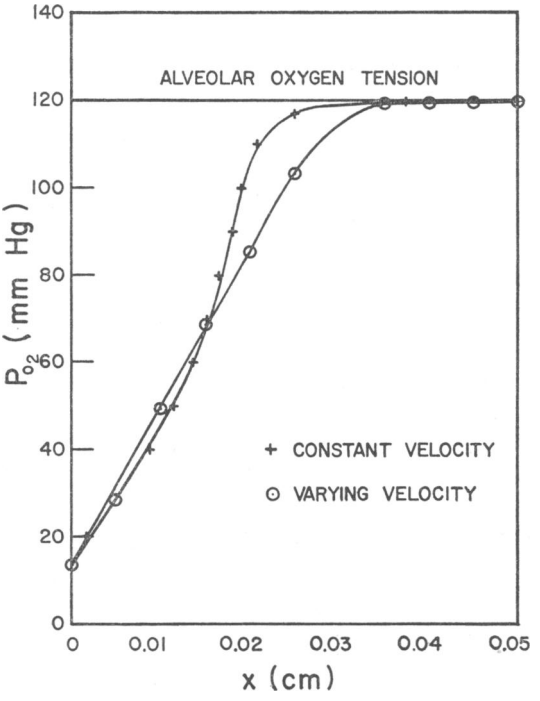

FIGURE 9 Average oxygen tension profiles for constant and time-varying flow rates, case (4)—heavy exercise, normal oxygen atmosphere.

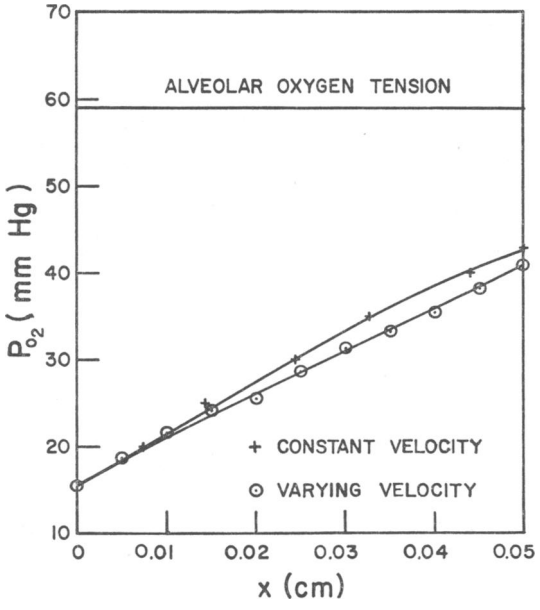

FIGURE 10 Average oxygen tension profiles for constant and time-varying flow rates, case (5)—heavy exercise, low oxygen atmosphere.

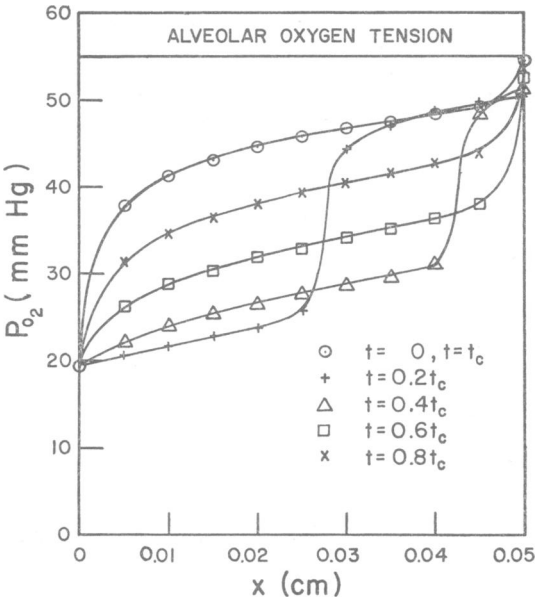

FIGURE 11 Instantaneous oxygen tension profiles for time-varying flow rate, case (3)—moderate exercise, low oxygen atmosphere. These curves are typical of those obtained in the other cases of this study.

taken into account, both in data used for calculations and in the model used to describe the gas exchange process.

Regional differences in blood flow and in ventilation have been shown to exist in the normal lung and to a greater extent in the diseased lung (20). This unevenness of the ventilation-perfusion ratio, also termed the "nonideality" of the lung, will cause an oxygen tension gradient to exist between alveolar gas and arterial blood (6). The total alveolar-arterial gradient of oxygen (*a-AD*) is a sum of the gradient due to diffusion effect and that due to "nonideality" effect, and the usual approach of investigators is to attempt to separate the two effects. Experimentally this is difficult to accomplish, but conceptually all one need do is to assume an ideal ventilation-perfusion ratio to examine the diffusion effect. This is the main justification for the assumption of an "ideal" lung. However, under certain physiological conditions, one of which is exercise, the differences in blood flow tend to even out (20) and the lung becomes more ideal, making the ideality assumption even better for the exercise cases in this study.

A study of nonideal distribution using a pulsatile capillary flow rate and a three compartment model of the total lung (20) would be the next step in a proper assessment of the effects of nonideal distribution on oxygen transport.

CONCLUSION

The effects of pulsatile flow of blood on oxygenation of blood in the pulmonary capillaries for an ideal lung was investigated using data for the membrane diffusing capacity of the lung and capillary volume for five combinations of exercise and

atmospheric oxygen content. The pulsatile flow was found to give substantially the same end capillary alveolar-arterial oxygen tension gradient as that found for a constant velocity model. In cases of breathing air, the pulsatile flow model gives over-all diffusing capacities 10–15% higher than the constant velocity model, but in low oxygen cases the over-all diffusing capacity was found not to be affected by pulsatile flow.

NOMENCLATURE

a—parameter in heartbeat function (see equation 5); controls height of velocity pulse, dimensionless
A—cross sectional area for flow of pulmonary capillaries, cm^2
$D_{M_{O_2}}$—membrane diffusing capacity for oxygen, ml O_2/min-mm Hg
$D_{L_{O_2}}$—over-all diffusing capacity of the lung for oxygen, ml O_2/min-mm Hg
$D_{L_{O_2}}(P(x))$—denotes the over-all diffusing capacity of the lung for oxygen as a function of oxygen tension, which, in turn, is a function of x
$f(P_{RBC})$—see equation 1
K—parameter in the heartbeat function, associated with average blood flow rate, cm^3/min
P—oxygen tension in general, mm Hg
P_A—alveolar oxygen tension, mm Hg
P_{RBC}—oxygen tension in the red blood cells, also termed oxygen tension in the blood, mm Hg
P_v—venous blood oxygen tension, mm Hg
$\dot{Q}_c$—cardiac output, cm^3/min
t—time, sec
t_c—period of heartbeat, sec
$u(t)$—velocity of blood in the capillaries, cm/sec (see equation 5)
V_c—volume of the capillaries, cm^3
X—distance down the capillary, cm
α_e—effective solubility of oxygen in the blood, ml O_2/ml blood-mm Hg
θ_{O_2}—diffusing capacity of the red blood cells, ml O_2/min-mm Hg-ml blood

Note Added In Proof. It was brought to our attention that it would be more appropriate to "bulk" average the P_{RBC} by means of the following expression

$$\bar{S}_{O_2}(x) = \frac{\int_0^{t_c} S_{O_2}(x, t) \cdot u(t)\, dt}{\int_0^{t_c} u(t)\, dt}$$

where $S_{O_2}(x, t)$ is the per cent saturation of oxygen at position x at time t, obtained from $P_{RBC}(x, t)$ by means of oxyhemoglobin dissociation curve. $P_{RBC}(x)$ will then be obtained from $\bar{S}_{O_2}(x)$ by a similar means. We have recalculated all the results by using this averaging method, and found that no appreciable changes are introduced thereby.

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